Metoprolol Comparison in Hypertensives) study in diabetic hypertensives showed maintained glycemic control and improved insulin resistance with carvedilol versus metoprolol (8). Similarly, nebivolol demonstrated improved insulin sensitivity when compared with metoprolol in hypertensive patients (9).

The authors incorrectly state that the European Society for Hypertension/European Society of Cardiology (ESH/ESC) is no longer endorsing beta-blockers as first-line therapy for hypertension. In actuality, ESH/ESC guidelines, published this year, maintain beta-blockers among the classes of drugs suitable for initiation and maintenance of blood pressure treatment (10). Furthermore, ESH/ESC and the American College of Clinical Endocrinologists recognize the differences that exist between agents in this class, distinguishing the vasodilatory beta-blockers from traditional ones in patients with metabolic risk factors.

We are not sure what the phenotype of an "uncomplicated" patient with hypertension is. Clearly, many with increased blood pressures have non-obstructive coronary and carotid plaques.

The use of beta-blockers in the treatment of patients with hypertension is deeply rooted in the knowledge of the role of the sympathetic nervous system in the pathophysiology of complications. We believe that recommendations for the use of beta-blockers in an individual with hypertension should be made after reviewing the totality of the data. Beta-blockers will continue to play a critical role in treatment of hypertension, and dismissing the entire class without fully examining the evidence might indeed amount to "throwing the baby out with the bath water."

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Please note: The authors are consultants and speak for the following pharmaceutical companies: Novartis, Merck, Forest, Bristol-Myers Squibb, Daiichi-Sankyo, Boehringer-Ingelheim, GlaxoSmithKline, and Sandoz.

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Reply

We thank Dr. Giles and colleagues for their interest in our paper (1) and completely agree with their contention that "recommendations for the use of beta-blockers in the individual with hypertension should be made after reviewing the totality of the data." Unfortunately, the totality in this case is completely negative. Ever since our meta-analysis about a decade ago, study after study has attested to the inefficacy of beta-blockers in hypertension. Why would any physician expose a hypertensive patient to a drug that reduces mortality no better than placebo, as evidenced in the thorough Cochrane meta-analysis (2), and yet leads to a withdrawal rate that is twice as high as the one seen with diuretics (which are certainly not the best-tolerated drug class for the treatment of hypertension)? We are puzzled by our colleagues' cherrypicking of the STOP-1 and -2 (Swedish Trial in Old Patients with Hypertension-1 and -2). Neither of those studies dared to conclude that beta-blockers per se reduce morbidity and mortality. The reason for this is very simply that neither one analyzed the effects of diuretics and beta-blockers separately. Thus, STOP-1 and -2 studies are classical examples of gin-and-tonic studies in which about two-thirds of patients treated with a beta-blocker also received a thiazide diuretic.

The INVEST (International Verapamil-Trandolapril Study) is a landmark trial in which an atenolol (given mostly twice a day)-based regimen was compared with a verapamil-based regimen, as Dr. Giles and colleagues point out. However, all of the patients in the INVEST study had well defined coronary artery disease, and an extrapolation from such a high-risk population to uncomplicated hypertension is not appropriate. As can be seen in our Figure 3 (1) we are convinced that coronary artery disease is an acceptable indication for the use of beta-blockers.

We use the term pseudoantihypertensive efficacy to describe the observation in the CAFE (Conduit Artery Function Evaluation) study (3) that, for a given brachial blood pressure, atenolol lowered central aortic blood pressure significantly less than did amlodipine. Therefore, practicing physicians may wrongly conclude that the patient has well controlled hypertension when central aortic pressure is still significantly elevated. The term pseudoantihypertensive efficacy aptly describes this phenomenon.

We certainly agree with our colleagues, and we have stated so (4), that vasodilating beta-blockers have a different hemodynamic profile and a different metabolic/endocrine profile, induce less weight gain (5), and are better tolerated than the traditional beta-blockers. Thus, nebivolol and carvedilol are not only better tolerated but also have the potential to be more beneficial in terms

of morbidity and mortality reduction than traditional beta-blockers. However, this potential remains hypothetic as long as we have no conclusive outcome studies attesting to this. If indeed the companies manufacturing these drugs are concerned about this issue they should mount outcome studies in hypertension. This does not need to be an exceedingly expensive endeavour, as is evidenced by the fact that it only took 1,473 patients with cerebrovascular disease to show that stroke reduction was no better with atenolol than with placebo (6).

We agree that many patients with increased blood pressure have some degree of nonobstructive coronary disease. However, neither our nor the Cochrane meta-analysis showed any efficacy of beta-blockers for primary prevention of coronary disease. The Cochrane meta-analysis specifically stated that "the absence of an effect on heart disease [compared with] placebo or no treatment" led to the conclusion that beta-blockers should not be used as first-line drugs in the treatment of hypertension.

We are not particularly concerned about "throwing out the baby with the bathwater." In 2006 more than 100 million prescriptions for beta-blockers were written in the U.S. Atenolol remains the fourth most prescribed drug, and most of these prescriptions are for atenolol given once a day for the treatment of hypertension. This is a sad state of the art, given the fact that atenolol has never shown to reduce morbidity and mortality in hypertension. One may also want to consider that treatment of 1,000 patients with beta-blockers for 4.4 years will result in 14 extra cases of diabetes, 3 extra deaths, and 5 extra strokes (7). This means that in the U.S. alone, beta-blocker therapy may account for 70,000 new cases of diabetes, 15,000 deaths, and 25,000 strokes every year.

Thus, many more gallons of bathwater can be thrown out before the baby runs any risk of being harmed.

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